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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,074	01/25/2007	David Fairlie	P1119/20002	1505

3000 7590 11/21/2008

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
11/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/596,074	FAIRLIE ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-139* is/are pending in the application.

4a) Of the above claim(s) *115-137 and 139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-114 and 138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/25/2007, 04/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 84-114 and 133 in the reply filed on 09/19/2008 is acknowledged.

Claims 115-137 and 139 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 09/19/2008.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 84-114 and 133 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are drawn to terms 'linking moiety', 'normal', zinc binding moiety that are vaguely defined.

The term 'linking moiety' appears 12 times in the specification. Closest to 'structural' information for linking moiety is found in paragraph [0142] shown below: As would be clear to a skilled **addressee** any number of **suitable** moieties can be used as the linking moiety of the compounds of the invention. It is typical, however, that the linking moiety is a hydrocarbyl moiety that is unbranched. Moieties of this type are the simplest to produce and are found to not interfere with the activity of the remainder of the compound. It is preferred that the linker has between 1 and 9 atoms in the normal chain, preferably between 1 and 4 atoms in the normal chain. It is unclear what structural element that are 'suitable' for the linking moiety is excluded.

Likewise, it is unclear what the term 'normal' means in the context of organic structure. According to the specification this 'group preferably contains from 2 to 20 carbons, preferably 2 to 12 carbons, most preferably 2 to 8 carbons in the normal chain'. It is if this group would exclude steroidal structure or materially different poly peptide chain containing 10 aminoacids.

Likewise, the zinc moiety is defined in the specification as follows:
zinc binding moiety containing at least one heteroatom

In addition the zinc binding moiety can be chosen so that it is any suitable moiety that will bind to zinc. In addition the zinc binding moiety can be chosen so that it is any suitable moiety that will bind to zinc. There are a number of suitable zinc binding moieties well known in the art. Examples of well known zinc binding moieties include sulfur donors (such as HS--R, wherein R is defined above), amine containing compounds (primary, secondary, tertiary amines), heterocyclic amines, carboxylates, amino acids, thiolates, dithiocarbamates, phosphorodidithiolates and the like. Some examples of suitable moieties within these subsets are as follows: Sulfur donors (thioproline, penicillamine, cysteine, 2-mercaptoethylamine, glutathione, methionine, thiosulfate, N-acetylcysteine, penicillaminedisulfide, thiomalate, and 2,3-dimercaptosuccinate Aliphatic amines (histamine, trien, Me4en)

Heterocyclic amines (pipicolate, nicotinate, picolinate, 8-hydroxyquinoline,bicinchoninate, bipy, phendisulfonate). Carboxylates (acetate, propionate, tartrate,

succinate, malate, gluconate, betahydroxybutyrate, lactate, salicylate, citrate, ascorbate, oxalate, EDTA) Amino acids (gly, arg, asn, glu, asp, glygly, glyglygly, glyglyhis, pro, 2,3-diaminopropionate, 2-amino-2-deoxygluconate, his). It is not the breadth of the claims that is unclear. Breadth of the claims is dealt later in the prosecution. It is unclear what is included or excluded. (Note: Database available to the Examiner is unable to complete a structure search for the instant claims).

Claim 99-103, 11-114 attempts to define structures by function, while structures can easily be represented by structural formulae and chemical names.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 84-114 and 133 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for few compounds corresponding to compounds of formula I wherein R1 is unsubstituted methylene units and M is hydroxamic acid moiety (that C(O)NHOH), does not reasonably provide enablement for plethora of structural possibilities claimed for R1 and M. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make **and use** the invention commensurate in scope with these claims.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

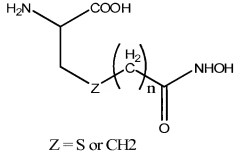
Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state

of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The claims are drawn to compounds of formula with several substituents layered on top of substituents encompassing zillions of conceivable structures that vary in physical and chemical properties such as size, molecular weight, logP, acidity and basicity, properties that are known in the art to greatly influence biological properties as well as PK and PD parameters that are relevant for the 'use aspect' of the claimed invention. As such the breadth of the claims defies art recognized concepts relating to productive small molecule-macromolecule interaction.

The chemistry direction provided in the specification is limited to amide derivatives of aminoacids



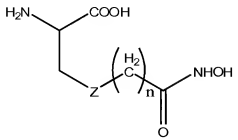
Z = S or CH2

There is no example in the specification wherein, the variable R1 is other than

what is shown above. While methods for making amides of aminoacids is well known to one skilled in the art, the plethora of structural possibilities for the claimed variable R1 would require undue experiment to one skilled in the art. Thus the statement on page 47, line 15-25 regarding skilled workers ability to compounds is not commensurate with the state of the organic chemical art. The unpredictability of in organic synthesis is high in spite of the high skill level in the area. The state of the art of organic chemical synthesis is closer to what is described by Dorwald et al. who states, "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and

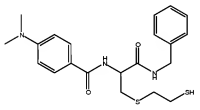
frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface]…….even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]…….. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]…….. As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8]……...Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, especially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]….." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

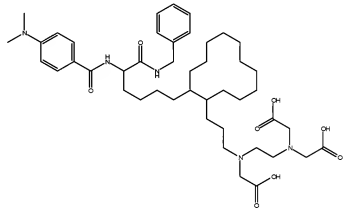
As to the "use aspect' of the enablement requirement, the disclosure is limited to amide derivatives of the aminoacids



Z = S or CH2

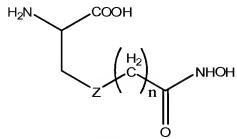
This drug design principles underlying such enabled compounds is consistent with what is known in the area of HDAC inhibitors. Two examples of embodiments encompassed by the formula I of instant claim are shown below:





Such widely differing structures as possibilities as HDAC inhibitors not only have no enabling support in the specification but also defies commonly accepted principles such as Structure-Activity-Relationship in medicinal chemistry art.

The quantity of experimentation: For the reasons presented above, there is a substantial gap between what is taught in the specification and what is being claimed. The working examples contain compounds all relating to a narrow Markush structure (of amide derivates of the aminoacids



Z = S or CH2

In addition, these narrowly definable, structurally similar compounds have shown a wide range of biological activity. Given that the specification does not disclose any SAR with respect to biological activity or because there is no disclosure in the specification with regards to applicant's 'minimum pharmacophore' for inhibitory activity, it is not clear what specific embodiments would be required for compounds to inhibit replicon activity. As such, one of ordinary skill in the art would be faced with undue amount of experimentation to identify the compound(s) buried in the zillion possibilities encompassed by the formula. The specification lacks disclosure sufficient to make and use the invention commensurate with the scope of the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states "**a patent is not a hunting license**. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

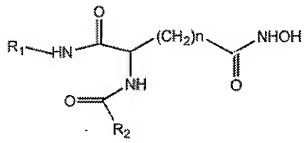
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 84-114 and 133 rejected under 35 U.S.C. 103(a) as being unpatentable over Richon et al. (WO/2003/032921, Publication date 04.24.2003,

WO/01/18171 A2, Publication date 03.15.2001) independently and further in view G. A. Patani and E.J. LaVoie, Bioiossterism: A rational Approach to Drug Design. Obviousness *Chem. Rev.* **1996**, *96*, 3147-3176.

Richon et al. teach HDAC inhibitor compounds of the following formula page 20,



wherein R_1 and R_2 are each selected from substituted or unsubstituted aryl (e.g., pheny, naphthyl), pyridineamino, 9-purine-6-amine, etc. encompassing compounds of the instant formula as HDAC inhibitors. These compounds correspond to compounds of the instant formula wherein Z is CH2,

Richon et al. does not teach all the possibilities for R1 and R2 as instantly claimed. Further, Richon et al. does not each compounds of the instant formula wherein Z is S.

The difference between the compounds of the instant claim and the compounds of the prior are, commonly used substituents on the aromatic rings of R1 and R2; Some of the compounds of Richon et al. are excluded in the instant claims by proviso. Further, the replacement of S for methylene units as isosteric replacement is well known in the art of medicinal chemistry because such a S

replacement for CH2 or CH2-CH2, especially in a aliphatic chain, does not alter the conformational flexibility or adversely affect the polarity of the molecule. Patani et al provide examples of such isosteric replacement technique for making alternate forms of known compounds with improved properties.

Therefore one of ordinary skill in the art of medicinal chemistry would be motivated to make the claimed compounds in searching for additional derivatives of the pharmacophore taught by Richon et al., using commonly employed substituents with reasonable expectation of success. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds of similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/
Primary Examiner, Art Unit 1625